light and to accommodation (30–40% incidence). Sweating was also reduced.

The incidence of ganglionic block over the various autonomic functions tested was different in every one of the 41 subjects for which complete records were obtained.

Variability in the response to a ganglion-blocking agent is as great in normal subjects as in patients. It may be regarded as a result of the varying autonomic constitution of different individuals.

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TREATMENT OF MURINE LEUKAEMIA WITH X RAYS AND HOMOLOGOUS BONE MARROW

PRELIMINARY COMMUNICATION

BY

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When mice are given an otherwise lethal dose of *x* rays to the whole body they can recover if injected intravenously with homologous myeloid cells. It is now established that their depleted haemopoietic and lymphopoietic tissues are colonized by cells derived from those which have been injected (Ford *et al.*, 1956). This suggests that leukaemia of the mouse might be successfully treated. On the one hand, the dose of *x* rays which is sufficiently lethal to normal cells of the bone marrow and lymphatic tissues to cause death of the animal might well be completely lethal to leukaemic cells: the irradiated animal could then be treated with normal isologous bone marrow from the same strain of mouse for the repopulation of the haemopoietic and lymphopoietic tissues. On the other hand, if the dose of *x* rays sufficient to kill the animal is not 100% lethal to leukaemic cells, the malignant condition would in these circumstances recur by growth from the surviving cells, since neither host nor graft has the ability to resist; but, if homologous bone marrow from a different strain of mouse were given, the colonizing cells might retain the capacity of the donor to destroy by the reaction of immunity these residual leukaemic cells—and perhaps also the host.

This preliminary communication deals with the results of three similar experiments designed to test the former hypothesis.

Experimental

Animals.—Mice of the CBA/H strain, inbred by strict sib-mating for many generations with frequent re-selection of sublines, were the test animals. They were three to four months old at the time of test. Mice of the same strain were used as isologous donors. Mice of an equally highly inbred A/H strain and hybrid mice, $T_6/+$ (Carter *et al.*, 1955), were homologous donors.

Tumour.—The leukaemia used in these experiments and nominated 151/1 was induced by means of chronic irradiation in a CBA mouse by our colleague, R. H. Mole. It can be passaged as a cell-suspension of spleen, lymph node, etc., to 100% of our CBA/H mice by intravenous and intraperitoneal injections of 10^6 cells. The response following subcutaneous injection is nearly 100%, but an occasional animal is resistant. When it has been given to the inbred strains, C_3H/H, A/H, C57/H, and 101/H, and to various types of hybrid mice using the same doses and routes, there have been no instances of leukaemia. In the CBA/H mouse it produces a generalized replacement of lymphoid tissue and bone marrow and an interstitial invasion of most other tissues with lymphoid cells resembling large lymphocytes. The leukaemia is relatively aleukaemic, the leucocyte count of peripheral blood being usually 20,000 to 50,000 per c.mm. Death from leukaemia in most cases occurs within one month of injection and certainly within two months in those animals in which the leukaemia has "taken." Survival for a period of three months has therefore been taken as test of cure.

As a routine the CBA/H mice were given 10^6 leukaemic cells in suspension in physiological saline containing 0.3% sodium citrate and were irradiated one week later.

X-radiation.—Acute doses were given in 14 minutes: the subacute doses were spread over 25 hours. In each case the quality of radiation was the same. The tube potential was 250 kV constant potential; H.V.L., 1.2 mm. Cu.

Results

For normal CBA/H mice given the *x*-irradiation in 14 minutes the LD_{98} is 950 rad.‡ The LD_{98} is 1,340 rad when the dose is spread over 25 hours.

CBA/H mice injected intravenously one week previously with 10^6 leukaemic cells, and then acutely irradiated with a dose of 950 rad and treated with isologous bone marrow or infant spleen, died after about a month with generalized leukaemia. (Mean survival of a group of 10 treated mice was 31.6 days (S.D. 8.0 days) from the time of irradiation, compared with 8.5 days (S.D. 2.6 days) of 10 unirradiated control mice.)

On the other hand, CBA/H mice injected one week previously with 10^6 leukaemic cells, irradiated over 25 hours to a dose of 1,500 rad, and then treated with bone marrow or infant spleen have shown survival of three months and longer in three successive experiments (see Table).

Animals Surviving (A) and Dying (†) After Treatment With Subacute Whole-body X-irradiation and Intravenous Bone Marrow

Experiment:	1	2		3
10^6 leukaemic cells given (date)	S.C. (14/3/56)	S.C. (26/4/56)	I.V. (26/4/56)	S.C. (24/5/56)
Unirradiated controls	†††††	††AA	††††	†††††
Experimental—(date)	(21–22/3/56)	(3–4/5/56)		(31/5–1/6/56)
1,500 rad *x* rays followed by bone marrow I.V. from mice:				
CBA/H	AAAAA AAAA†	AAAAA	AAA††*	AAA††
A/H	—	—	—	AA†* †* †*
T_6 +	—	—	—	AAA†* †*

S.C. = Subcutaneously. I.V. = Intravenously.
* Deaths not attributable to leukaemia.

In experiment 1, in which the leukaemia was induced by subcutaneous injection, 9 out of 10 treated mice have survived for over five months; all are in good general condition and are apparently normal apart from grey hair. The tenth

‡The doses are recorded as rads estimated in soft tissue.

mouse died after seven weeks of leukaemia with a local tumour in the iliac region. All the untreated controls were dead within 21 days.

In experiment 2, half the animals were given the leukaemia by the subcutaneous route. All five of the treated animals survive and are well but grey. Two untreated control animals also survive: these mice are in all probability sibs, and their failure to "take" the leukaemia can perhaps be ascribed to genetic drift. Of the five animals given the leukaemia intravenously, two treated animals died, one of generalized leukaemia after 19 days and one from an undetermined cause after 45 days; the other three are apparently well. The controls were dead within 17 days.

In experiment 3, homologous as well as isologous marrow was given as restorative treatment. Three of the five animals treated with isologous marrow survive, two having died after 36 and 44 days with generalized leukaemia. Three of the five mice given the homologous marrow from strain A/H mice died between one and two months after treatment. They were wasted and had diarrhoea. These deaths are attributed to complications of the treatment and not to its failure, but the detailed pathological processes are not yet understood. Of the five animals treated with $T_6/+$ bone marrow, three are well and two died within six days of the treatment, death presumably being due to the effects of radiation. Passage of the tissues of one of these to two normal CBA/H mice failed to reveal any leukaemia. All controls died within 26 days.

Discussion

The results show that this particular leukaemia (151/1) of the CBA mouse is not cured by the 950-rad dose of *x* rays given to the whole body in a single short exposure. When, however, the dose is increased to 1,500 rad and the time extended to 25 hours, in a proportion of cases the leukaemia is eliminated and recovery of the animal from the general radiation syndrome may be effected by treatment with intravenous bone marrow. Previous experience in this laboratory (Barnes and Loutit, 1955) would indicate that for this purpose isologous CBA/H bone marrow would be superior to homologous bone marrow from strain A, and this is borne out by the limited data in experiment 3, where mice given strain A/H bone marrow, though apparently cured of leukaemia, died following chronic diarrhoea. This agrees with other observations, to be published, that homologous bone marrow from strains A, C_3H, and C57 and from the hybrid mice $T_6/+$ given to leukaemic mice after 950 rad of *x* rays as an acute dose results in death from this same syndrome.

These preliminary experiments are reported because they showed some promise of the successful treatment of murine leukaemia. The results need confirmation with other types of leukaemia in other strains of mice, and different schedules of treatment may well provide more favourable results. If the experiences of several laboratories could be pooled some general laws might be evolved which should help in planning an extrapolation from mouse to man for treatment of those types of leukaemia which are so rapidly fatal as to warrant the use of desperate measures.

Summary

A generalized lymphoid leukaemia (151/1) of the CBA mouse can be transmitted by passage of cells intravenously or subcutaneously. One week after receiving such tissue mice were given *x*-irradiation to the whole body in doses approximating to the LD_{100}. They were then treated with intravenous injections of isologous (CBA) myeloid tissue and a few with homologous bone marrow from other strains of mice in order to recolonize haemopoietic and lymphopoietic tissue. Given 950 rads at high intensity (14 minutes), the mice were not cured of leukaemia, but when the dose was 1,500 rads in 25 hours there have been 25 survivors out of 35 after three months.

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ADRENALECTOMY FOR INTRACRANIAL METASTASES FROM CARCINOMA OF THE BREAST

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It is now generally recognized that bilateral gonadectomy with bilateral adrenalectomy often leads to a regression of metastatic carcinoma of the breast and gives results which are well worth while. A course of hormone treatment by androgens (or by oestrogens in the male) should usually precede the operation. There seems, however, to be a widely held opinion (not shared by us) that the presence of cerebral metastases contraindicates surgical treatment because of the poorness of the results, although we could not discover a definite statement to this effect in the literature. Huggins and Dao (1953) describe a series of 53 adrenalectomies (51 females, 2 males) in which only two had cerebral metastases. This may have been due to the fact that such cases were not generally submitted to operation. Neither of these two (one female and one male) responded to operative treatment. Galante *et al.* (1954), however, reported regression of the secondaries in the only case with cerebral metastases (a female) in their series of 31 patients who were submitted to operation. Cade's (1955a, 1955b) series of 100 adrenalectomies (one male) contained no definite example of cerebral metastases, though cases were not excluded for that reason. A few had metastases involving the base of the skull and cranial nerves, and among these there were some satisfactory results (Cade, 1956, personal communication). Similarly, Pyrah and Smiddy (1954), reporting 22 cases (one male), submitted no case with cerebral metastases to operation.

At the Royal Marsden Hospital over 90 adrenalectomies had been done up to the end of 1955. In only two patients were cerebral metastases clinically evident. They are reported here. Both have responded very favourably.

Case 1

In August, 1948, a married woman, then aged 37, had a radical mastectomy done for anaplastic carcinoma of the left breast, not involving the axillary lymph nodes. She was first seen at the Royal Marsden Hospital in January, 1951, with carcinoma of the whole of the right breast, with peau d'orange and a retracted nipple and extensive involvement of the axillary nodes. Bilateral oophorectomy